PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 07 March 2001 (07.03.01)	
International application No. PCT/SE00/01495	**Applicant's or agent's file reference** 55843-60890
International filing date (day/month/year) 14 July 2000 (14.07.00)	**Priority date** (day/month/year) 14 July 1999 (14.07.99)
Applicant JOHANSSON, Roger	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 February 2001 (14.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

BERG, S., A.
Albihns Stockholm AB
P.O. Box 5581
S-114 85 Stockholm
SUÈDE

Date of mailing (day/month/year) 07 March 2001 (07.03.01)	
Applicant's or agent's file reference 55843-60890	**IMPORTANT NOTIFICATION**
International application No. PCT/SE00/01495	**International filing date** (day/month/year) 14 July 2000 (14.07.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
BERG, S., A. Albihns Patentbyrå Stockholm AB P.O. Box 5581 S-114 85 Stockholm Sweden		
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
BERG, S., A. Albihns Stockholm AB P.O. Box 5581 S-114 85 Stockholm Sweden		
	Telephone No. +46 8 59 88 72 00	
	Facsimile No. +46 8 59 88 73 00	
	Teleprinter No.	

3. Further observations, if necessary:
The new agent's address on the Demand has been considered as a change under Rule 92bis. In case of disagreement, the International Bureau should be notified immediately.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
55843-60890		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01495	14.07.2000	14.07.1999
International Patent Classification (IPC) or national classification and IPC7		
A 61 M 1/00, A 61 M 25/095		
Applicant		
CMA/MICRODIALYSIS AB		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14.02.2001	22.10.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Inger Löfgren/Els Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01495

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-7 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under article 19
pages _____ , filed with the demand
pages 1-2 , filed with the letter of 04.09.2001

☒ the drawings:
pages 1-3 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01495

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims	1-8	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Cited documents:
D1: US5782764
D2: US4989608

D1 shows a method and a means for positioning a medical instrument in a tissue. The instrument has a carbon-fibre or glass-fibre composite body, which preferably carries a contrast agent, which is appropriate to the particular imaging modality to be used with the instrument. In some preferred embodiments, the contrast agent is a paramagnetic metal ion. In other preferred embodiments the contrast agent is a preparation, containing micro-bubbles of air or other gas, or the contrast region includes an air-filled void.

The invention differs in that the claimed medical instrument and the positioning indicating means are particularly adapted for micro dialysis. The arrangement involves sealing the distal end of the micro dialysis probe in the presence of a position- indicating object. The position- indicating object comprises x-ray opaqueness or visibility when using NMR.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2 shows a device construction facilitating the visibility of a device when inserted into a body being subjected to magnetic resonance imaging. The device carries material exhibiting a characteristic under magnetic resonance imaging, which differs substantially from that of the body so that the visibility of the device under magnetic resonance imaging is substantially enhanced. A method for imaging foreign objects in a body having tissue by the use of magnetic resonance imaging and x-ray imaging is also shown. The method comprises the steps of causing the foreign object to carry at least one material, causing the foreign object to exhibit a characteristic under magnetic resonance imaging, which differs from the characteristic of the tissue of the body, to enhance the visibility of the foreign object when positioned in the body and also to exhibit a characteristic under x-ray imaging.

The claimed invention differs in that the micro-dialysis probe only is intended to comprise one visualising object. The position- indicating object comprises x-ray opaqueness or visibility when using NMR.

The claimed invention according to claims 1 - 8 is not considered to be obvious in view of what is known from D1 and D2. None of the documents or any relevant combination of them reveal a micro dialysis probe as described by these claims.

According to the arguments stated above, the invention claimed in claims 1-8 is novel, considered to involve an inventive step and have industrial applicability.

PATENT COOPERATION TREATY

PCT

RECD 31 OCT 2001
PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
55843-60890		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01495	14.07.2000	14.07.1999
International Patent Classification (IPC) or national classification and IPC7		
A 61 M 1/00, A 61 M 25/095		
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CMA/MICRODIALYSIS AB		

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3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
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Date of submission of the demand	Date of completion of this report
14.02.2001	22.10.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Inger Löfgren/Els Telephone No. 08-782 25 00

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pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
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☒ the drawings:
pages 1-3 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☐ the sequence listing part of the description:
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☐ furnished subsequently to this Authority in computer readable form.

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☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE00/01495

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1. Statement

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	Claims		NO
Inventive step (IS)	Claims	1-8	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

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The invention differs in that the claimed medical instrument and the positioning indicating means are particularly adapted for micro dialysis. The arrangement involves sealing the distal end of the micro dialysis probe in the presence of a position- indicating object. The position- indicating object comprises x-ray opaqueness or visibility when using NMR.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

D2 shows a device construction facilitating the visibility of a device when inserted into a body being subjected to magnetic resonance imaging. The device carries material exhibiting a characteristic under magnetic resonance imaging, which differs substantially from that of the body so that the visibility of the device under magnetic resonance imaging is substantially enhanced. A method for imaging foreign objects in a body having tissue by the use of magnetic resonance imaging and x-ray imaging is also shown. The method comprises the steps of causing the foreign object to carry at least one material, causing the foreign object to exhibit a characteristic under magnetic resonance imaging, which differs from the characteristic of the tissue of the body, to enhance the visibility of the foreign object when positioned in the body and also to exhibit a characteristic under x-ray imaging.

The claimed invention differs in that the micro-dialysis probe only is intended to comprise one visualising object. The position- indicating object comprises x-ray opaqueness or visibility when using NMR.

The claimed invention according to claims 1 - 8 is not considered to be obvious in view of what is known from D1 and D2. None of the documents or any relevant combination of them reveal a micro dialysis probe as described by these claims.

According to the arguments stated above, the invention claimed in claims 1-8 is novel, considered to involve an inventive step and have industrial applicability.

The Swedish Patent Office
PCT International Application

PCT/SE 00/01495
04 -09- 2001

Claims

1. A microdialysis probe, comprising a dialysis membrane (115) located and supported between a closed distal end of the probe and a proximal end of the same, said membrane (115) essentially surrounding a first tube (116), said first tube and said membrane being so arranged, that a space (118) for passage of perfusion liquid is formed therebetween; said first tube exhibiting at least one through-hole for the passage of the perfusion liquid near the distal end of the first tube, said probe having inlet and outlet means (107,108) for perfusion liquid, **characterized** by the distal end of the space (118) being sealed in the presence of a position indicating object (130,410) imparting such characteristics to the distal part of the probe as to allow non-invasive examination of the location of the distal part of the microdialysis probe.

2. A microdialysis probe according to claim 1, **characterized** in said position indicating object being an x-ray opaqueness giving object.

3. A microdialysis probe according to claim 1, **characterized** in said position indicating object being an object made from gold.

4. A microdialysis probe according to claim 1, **characterized** in said position indicating object being an object visible when using NMR (Nuclear Magnetic Resonance).

5. A microdialysis probe according to any of the preceding claims **characterized** in that the distal end of the first tube (116) being sealed by means of a glue which holds and seals a plug (130) which comprises the position indicating object (130,410).

The Swedish Patent Office
PCT International Application

6. A microdialysis probe according to claim 1, 2 or 4, **characterized** in that said position indicating object is a plug made of any bio-compatible metal, alloy or amorphous compound which imparts the x-ray opaqueness necessary.

7. A microdialysis probe according to claim 1, 2 or 4, **characterized** in that said position indicating object is a plug made of compound dispersed in the glue sealing the probe which imparts the x-ray opaqueness to the plug.

8. A microdialysis probe according to claim 1 or 3, **characterized** in that said position indicating object is a hollow object filled with air or the like.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
18 January 2001 (18.01.2001)

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(10) International Publication Number
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(30) Priority Data:
9902695-7 14 July 1999 (14.07.1999) SE

(71) Applicant *(for all designated States except US)*: **CMA/MICRODIALYSIS AB** [SE/SE]; Box 2, S-171 18 Solna (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **JOHANSSON, Roger** [SE/SE]; Valloxvägen 14, S-741 42 Knivsta (SE).

(74) Agents: **BERG, S., A.** et al.; Albihns Patentbyrå Stockholm AB, P.O. Box 5581, S-114 85 Stockholm (SE).

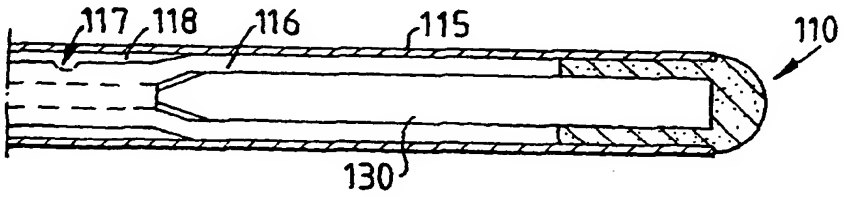
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MICRODIALYSIS PROBE



(57) Abstract: The invention concerns a microdialysis probe, comprising a dialysis membrane (115, 415) located and supported between a closed distal end of the probe and a proximal end of the same, said membrane (115, 415) essentially surrounding a space (118, 418) for passage of perfusion liquid; said probe having inlet and outlet means (107, 108; 407, 408) for perfusion liquid, characterized by presence of a position indicating object imparting such characteristics to the distal part of the probe as to allow non-invasive examination of the location of the distal part of the microdialysis probe.

WO 01/03752 A1

Microdialysis probe.

FIELD OF THE INVENTION

The invention relates to a microdialysis probe. Microdialysis probes of this kind are described in SE-C-434 214, US,A,5,735,832 and US,A,5,741,284.

The meaning of specific wordings in this text should be interpreted as follows:
The word probe should be interpreted also as catheter.
The inlet and outlet of the probe as described may in case of a reversed flow be used as outlet and inlet, respectively.
Perfusion liquid is the liquid used in the microdialysis, which is allowed to enter the probe and there take up substances from the surrounding tissue through a membrane. The perfusion liquid becomes the dialysate after the dialysis.
Non-invasive investigating examination in this document refers to e.g. X-ray, NMR or the like techniques.

BACKGROUND OF THE INVENTION

Microdialysis is a method of examination in which a probe is inserted into tissue in vivo, such that one side of a semi-permeable membrane is in contact with tissue and extra cellular liquid and the other side is flushed or rinsed with a dialysis liquid (perfusate) which takes-up substances from the extra cellular liquid through the membrane. These substances can then be analyzed in the dialysate on or after exiting the probe.

Microdialysis probes are by nature fragile and very small, which requires great care in inserting and withdrawing the probe from the tissue in which it is used. However, it is also of great importance that the probe when inserted into tissue of a living person, is placed in the intended location such that when measuring the probe actually through microdialysis measures the intended chemical/biological variables that at each measurement is of interest. It is of course important in these measurements to know exactly what is measured.

The use of microdialysis becoming more frequent and common raises other problems such as monitoring and control of the probe during insertion and use. It is a fact that microdialysis provides a unique possibility to examine the equilibrias of substances and/or the amounts present or missing of substances or to monitor specific changes in the status of substances connected with e.g. the use of medicaments, in surgery etc.

The monitoring and control of the probe position during insertion/withdrawal and use has been an obstacle in so far that the smallness and the material of the probe does not make possible the use of common methods for detecting the probe once the insertion has been started. This becomes more problematic the deeper into the tissue the microdialysis is to take place.

SUMMARY OF THE INVENTION.

It is thus an object of the invention is to provide a microdialysis probe, the location of which may be monitored and controlled using means such as X-rays or the like during insertion/withdrawal or during dialysis in order to facilitate the placement of the probe at a predetermined location and to control the location of the probe.

It is also an object of the invention to provide a microdialysis probe, which is suitable for the general use in living tissue when taking samples for e.g. diagnostic purposes.

In accordance with the invention, these and other objects evident from the description of the invention are accomplished in a microdialysis probe in that characterized by presence of a position indicating object imparting such characteristics to the distal part of the probe as to allow non-invasive examination of the location of the distal part of the microdialysis probe.

BRIEF DESCRIPTION OF THE DRAWINGS.

The invention will now be described by way of example and with reference to the accompanying drawings in which:

Fig. 1 shows, partially in section, a first embodiment of a microdialysis probe in section according to the invention.

Fig. 2 shows a detailed view of the foremost part of the probe according to the embodiment as shown in Fig. 1.

Fig. 3 a - c shows in detail the sealing of the most distal part of the first tube according to the embodiment shown in Fig. 1 and Fig.2.

Fig. 4 shows a second embodiment of a microdialysis probe in section according to the invention.

DETAILED DESCRIPTION OF PREFERRED FORMS OF THE INVENTION.

A first embodiment of the microdialysis probe according to the invention is shown in Fig. 1 and Fig 2. The probe exhibits a distal end piece 110 comprised of glue which holds and seals a plug 130 within the distal part of a membrane 115. This comprises the foremost tip of the probe. The membrane 115 is preferably tubular. A proximal tubular fitting 111and a proximal end piece 113 comprises the other end of the probe as such. The proximal tubular fitting 111 is permanently fastened to a proximal end piece 113. The proximal end of the membrane 115 is fastened to the proximal tubular fitting 111.

In the proximal end piece 113 two tubes 107 and 108 constituting the inlet to the probe and the outlet from the probe are connected to the probe, such as to let the perfusion liquid pass through the same. Note in the definitions above the possibility of reversed flow.

Within the membrane 115, which is in the form of a tube made from semi-permeable material, and also within the proximal tubular fitting 111, a first tube 116 extends essentially from the proximal end of the probe to the distal end. The first tube 116 is closed at the most distal end by a position indicating object, *a* plug 130, and exhibits at least one aperture 117 at or near the distal end. The aperture 117 constitutes a passage for the perfusion liquid entering the space 118 defined by the first tube 116 and the dialysis membrane 115 in combination with the proximal tubular fitting 111 and the distal tubular fitting 112. For the withdrawal of the perfusion liquid a second tube 119 extends from the proximal end of the probe and opens up into the same space 118 somewhere near to the to the proximal end of the probe thereby forming an exit for the perfusion liquid. The perfusion liquid has now become a dialysate having acquired substances exchanged over the semi-permeable membrane. The distal end piece 110 of the probe may e.g. be fastened in a permanent way to the distal end of the first tube 116.

To give a proper understanding of the invention, exemplary dimensions are given here. The length of the probe may be e.g. 5 cm from the most distal end of the same to the proximal part of the proximal tubular fitting 111. The length of the tubular fitting may be approximately 2 cm, thus the length of the membrane may be approximately 3 cm. The diameter of the proximal tubular fitting may be approximately 1 mm and the outer diameter of the membrane may be approximately 0.6 mm.

The plug 130 shown in Fig. 2 may preferably be manufactured from gold. Other materials may of course be used but the reason for using gold is the ductility and the relative opaqueness for X-rays and also the chemical and physiological inertness exhibited by gold.

In a second embodiment the plug 130 may be made such as to make the distal end of the microdialysis probe visible during examination using NMR (Nuclear Magnetic Resonance).

This plug could e.g. have the form of a hollow amorphous plug filled with air or the like, which would impart characteristics to the plug such that it will be possible to locate the plug using NMR.

One way of accomplishing the sealing at the distal end of the first tube 316 is shown in Fig 3 a - c.

In Fig. 3a) the form of an exemplary first tube 316 according to the invention is shown. The tube has been subjected to corbelling in order to widen the diameter of the same enough to accommodate the sealing plug 330.

In Fig. 3 b) a preferred embodiment of the sealing plug 330 is shown and in Fig. 3c) the first tube 316 with the sealing plug 330 in place is shown.

A second embodiment of the microdialysis probe according to the invention is shown in Fig. 4. The probe exhibits a distal end piece 410 and a distal tubular fitting 412. The distal tubular fitting 412 in combination with the end piece 410 comprises the foremost tip of the probe. A proximal tubular fitting 411 and a proximal end piece 413 comprises the other end of the probe as such. The proximal tubular fitting 411 is permanently fastened to a proximal end piece 413. A membrane 415 is fastened to the distal tubular fitting 412, the membrane 415 having a smaller diameter than the fitting. The membrane is preferably tubular. The fitting itself being closed at the most distal end thereof e.g. by using glue or the like, forming the distal end 410. The other end of the membrane 415 is fastened to the proximal tubular fitting 411.

In order to accomplish an X-ray opaqueness of the foremost part of the probe the distal end may be formed as a half-sphere or the like from a material which is opaque to X-rays or the X-ray opaqueness creating material may be incorporated in the glue as such.

In the end proximal piece 413 two tubes 407 and 408 constituting the inlet to the probe and the outlet from the probe are connected to the probe, such as to let the perfusion liquid pass through the same. Note above the possibility of reversed flow.

In this embodiment the dimensions of the probe will be approximately the same as in the embodiment described in connection with Fig 1.

Within the membrane 415, which is in the form of a tube made from semi-permeable material, first tube 416 extends essentially from the proximal end of the probe to the distal end. The first tube 416 has a closed distal end and has at least one aperture 417 at or near the distal end. The aperture 417 constitutes a passage for the perfusion liquid entering the space 418 defined by the first tube 416 and the dialysis membrane 415 in combination with the proximal tubular fitting 411 and the distal tubular fitting 412. For the withdrawal of the perfusion liquid a second tube 419 extends from the proximal end of the probe and opens up into the same space 418 somewhere near to the to the proximal end of the probe thereby forming an exit for the perfusion liquid.

In the same manner as has been described in connection with the first embodiment of the invention the end piece 410 sealing distal end of the probe may be made such as to make the same visible during examination using NMR (Nuclear Magnetic Resonance). This could e.g. be done by incorporating in the sealing glue a hollow amorphous plug filled with air or the like, which would impart characteristics to the distal end of the probe such that it will be possible to locate the probe end by using NMR.

The invention has been described under reference to embodiments of the same. It should be understood that the above describes an exemplary embodiment of the distal end of the probe itself and the constructive details thereof may vary within the scope of the claims or be independent of the constructive details of the distal end of

the probe depending on different embodiments of the invention. The scope of the invention however is described by the appended claims.

Claims

1. A microdialysis probe, comprising a dialysis membrane (115,215) located and supported between a closed distal end of the probe and a proximal end of the same, said membrane (115,215) essentially surrounding a space (118,218) for passage of perfusion liquid; said probe having inlet and outlet means (107,108; 207,208) for perfusion liquid, **characterized** by presence of a position indicating object (130,410) imparting such characteristics to the distal part of the probe as to allow non-invasive examination of the location of the distal part of the microdialysis probe.

2. A microdialysis probe according to claim 1, **characterized** in said position indicating object being an x-ray opaqueness giving object.

3. A microdialysis probe according to claim 1, **characterized** in said position indicating object being an object visible when using NMR (Nuclear Magnetic Resonance).

4. A microdialysis probe according to any preceding claim, **characterized** in a first tube for inlet of perfusion liquid into the space between the membrane and the first tube, said first tube exhibiting a through-hole for the passage of the perfusion liquid near the distal end of the first tube, said most distal end of the first tube being sealed by a plug of said position indicating object.

5. A microdialysis probe according to claim 1, 2 or 4, **characterized** in that said position indicating object is a plug made of gold.

6. A microdialysis probe according to claim 1, 2 or 4, **characterized** in that said position indicating object is a plug made of any bio-compatible metal, alloy or amorphous compound which imparts the x-ray opaqueness necessary.

7. A microdialysis probe according to claim 1, 2 or 4, **characterized** in that said position indicating object is a plug made of compound dispersed in the glue sealing the probe which imparts the x-ray opaqueness to the plug.

8. A microdialysis probe according to claim 1 or 3, **characterized** in that said position indicating object is a hollow object filled with air or the like.

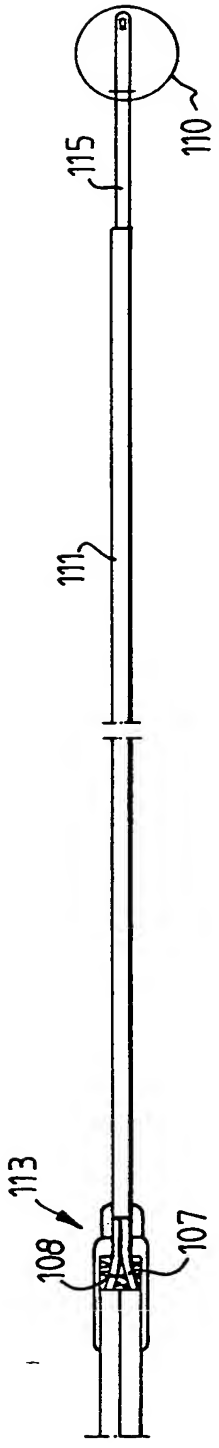


FIG.1

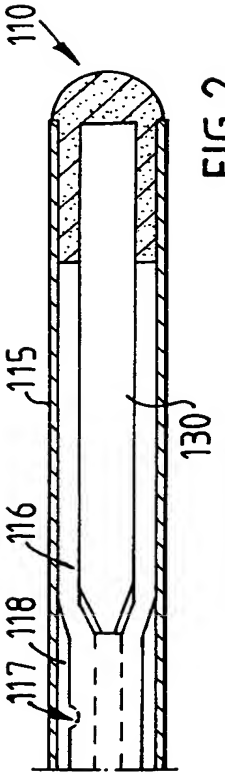


FIG.2

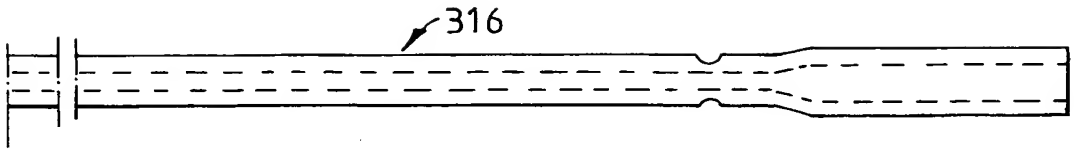


FIG. 3a

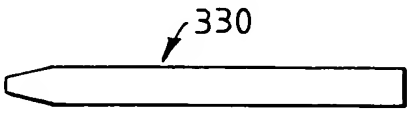


FIG. 3b

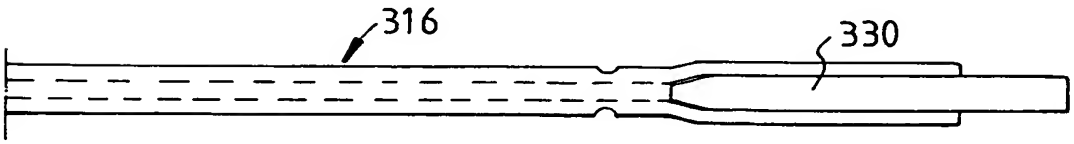


FIG. 3c

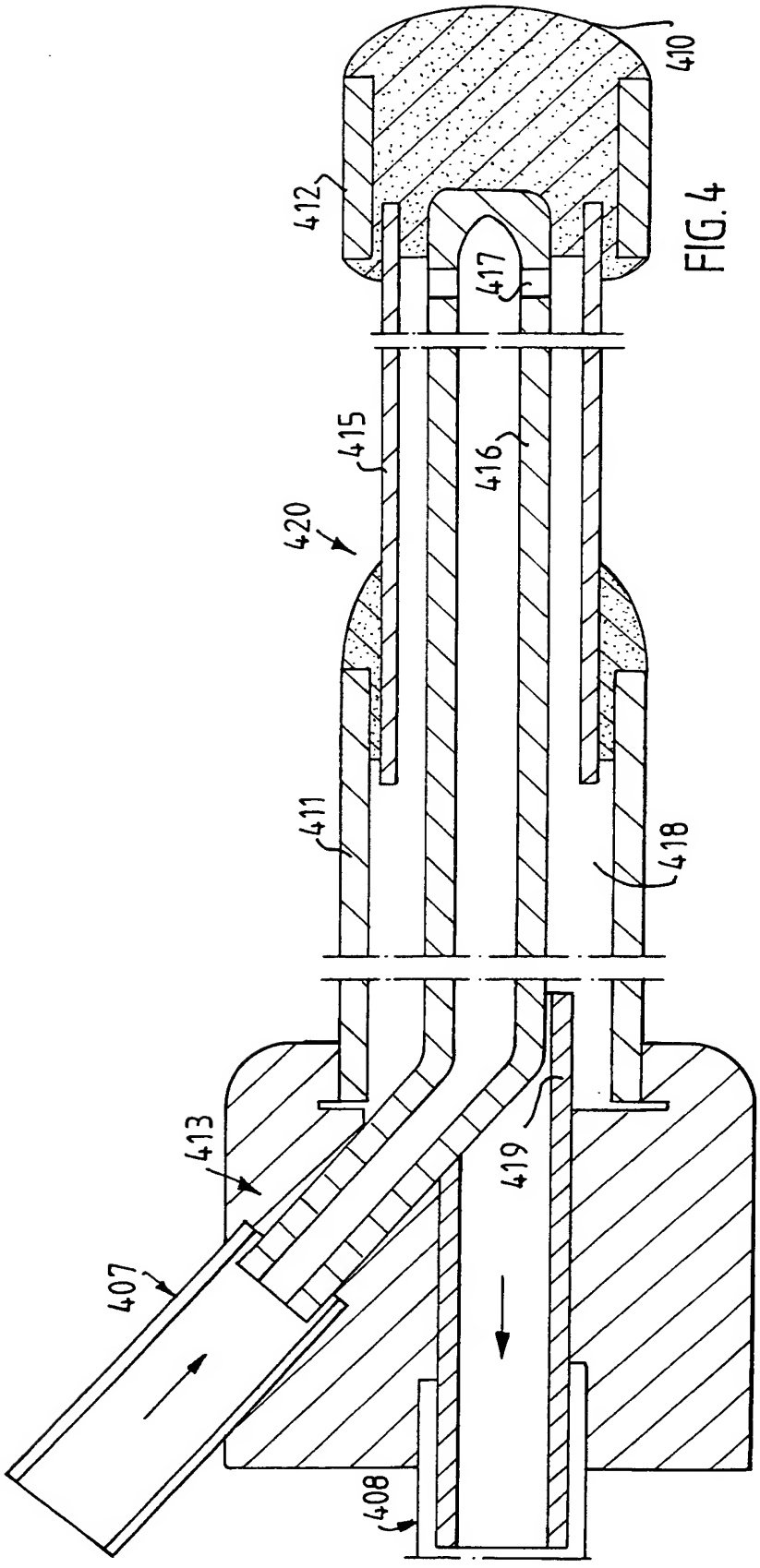


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01495

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61M 1/00, A61M 25/095
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61M, A61B, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5782764 A (WERNE), 21 July 1998 (21.07.98), column 1, line 29 - column 2, line 22; column 5, line 37 - line 64	1-8
X	US 4989608 A (RATNER), 5 February 1991 (05.02.91), column 4, line 12 - line 35; column 7, line 41 - column 8, line 63	1-8
A	US 5441481 A (MISHRA ET AL), 15 August 1995 (15.08.95)	1-8
A	US 5817017 A (YOUNG ET AL), 6 October 1998 (06.10.98)	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 October 2000	26-10-2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Inger Löfgren/MP Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01495

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5735832 A (KARLSSON), 7 April 1998 (07.04.98), column 2, line 13 - line 34 -- --------	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/08/00

International application No.
PCT/SE 00/01495

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5782764 A	21/07/98	EP 0859965 A	26/08/98
		US 5744958 A	28/04/98
		WO 9717622 A	15/05/97
		AU 3592597 A	10/06/98
		WO 9822022 A	28/05/98
US 4989608 A	05/02/91	US 5154179 A	13/10/92
US 5441481 A	15/08/95	AU 2654995 A	21/12/95
		CA 2191303 A	07/12/95
		WO 9532746 A	07/12/95
US 5817017 A	06/10/98	AU 680248 B	24/07/97
		AU 6631994 A	08/11/94
		EP 0750520 A	02/01/97
		JP 8509141 T	01/10/96
US 5735832 A	07/04/98	AU 1722495 A	21/08/95
		AU 6694494 A	21/11/94
		CA 2181582 A	10/08/95
		CN 1140416 A	15/01/97
		DE 69404983 D,T	29/01/98
		EP 0696375 A,B	14/02/96
		EP 0742725 A	20/11/96
		FI 105060 B	00/00/00
		FI 955126 A	27/12/95
		FI 963075 A	02/08/96
		JP 9508303 T	26/08/97
		NO 954284 A	26/10/95
		NO 962987 A	17/07/96
		SE 502438 C	16/10/95
		SE 9400377 A	05/08/95
		US 5678917 A	21/10/97
		WO 9520983 A	10/08/95
		SE 9500095 A	13/07/96